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Delaying the Empiric Treatment of *Candida* Bloodstream Infection until Positive Blood Culture Results Are Obtained: a Potential Risk Factor for Hospital Mortality

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Fungal bloodstream infections are associated with significant patient mortality and health care costs. Nevertheless, the relationship between a delay of the initial empiric antifungal treatment until blood culture results are known and the clinical outcome is not well established. A retrospective cohort analysis with automated patient medical records and the pharmacy database at Barnes-Jewish Hospital was conducted. One hundred fifty-seven patients with a *Candida* bloodstream infection were identified over a 4-year period (January 2001 through December 2004). Fifty (31.8%) patients died during hospitalization. One hundred thirty-four patients had empiric antifungal treatment begun after the results of fungal cultures were known. From the time that the first blood sample for culture that was positive was drawn, 9 (5.7%) patients received antifungal treatment within 12 h, 10 (6.4%) patients received antifungal treatment between 12 and 24 h, 86 (54.8%) patients received antifungal treatment between 24 and 48 h, and 52 (33.1%) patients received antifungal treatment after 48 h. Multiple logistic regression analysis identified Acute Physiology and Chronic Health Evaluation II scores (one-point increments) (adjusted odds ratio [AOR], 1.24; 95% confidence interval [CI], 1.18 to 1.31; $P < 0.001$), prior antibiotic treatment (AOR, 4.05; 95% CI, 2.14 to 7.65; $P = 0.028$), and administration of antifungal treatment 12 h after having the first positive blood sample for culture (AOR, 2.09; 95% CI, 1.53 to 2.84; $P = 0.018$) as independent determinants of hospital mortality. Administration of empiric antifungal treatment 12 h after a positive blood sample for culture is drawn is common among patients with *Candida* bloodstream infections and is associated with greater hospital mortality. Delayed treatment of *Candida* bloodstream infections could be minimized by the development of more rapid diagnostic techniques for the identification of *Candida* bloodstream infections. Alternatively, increased use of empiric antifungal treatment in selected patients at high risk for fungal bloodstream infection could also reduce delays in treatment.

Nosocomial bloodstream infections are serious infections associated with significant mortality and health care costs (39). Fungal bloodstream infections, primarily those caused by *Candida* species, are now the fourth most common bloodstream infection in the United States (21, 29, 30, 42). Risk factors for the development of *Candida* bloodstream infection are well recognized and include previous administration of antimicrobial agents (4, 33, 40), corticosteroids (14, 16), or chemotherapeutic agents (14, 16, 34); hematologic or solid-organ malignancy (16); neutropenia (14, 41); extensive intra-abdominal surgery or burns (3, 14, 16); mechanical ventilation or admission to an intensive care unit (2, 4, 25, 28, 33, 37); indwelling central venous catheter or parenteral nutrition (2–4, 14, 16, 40); hemodialysis (40); and prior fungal colonization (4, 14, 28, 37, 40, 41). More recently, there has been an increase in the number of non-*Candida albicans Candida* species associated with bloodstream infection (1, 36). Prior patient exposure to antifungal therapy, particularly with fluconazole, appears to be a predictor for bloodstream infection with non-*C. albicans Candida* species (9, 29, 35).

Appropriate initial antimicrobial therapy has been shown to be an important predictor of outcome for patients with microbiologically confirmed nosocomial infections, including bloodstream infections and severe sepsis (8–13, 17–20). One group of investigators has been able to demonstrate a significant relationship between the percentage of inappropriate initial antimicrobial treatment administered for the treatment of nosocomial bloodstream infections caused by specific pathogens, including *Candida* species, and overall hospital mortality (12). Unfortunately, most prior studies of *Candida* bloodstream infection have not specifically evaluated the role of delayed appropriate antimicrobial therapy on clinical outcomes.

Due to the overall importance of bloodstream infections attributed to *Candida* species, we performed a retrospective cohort analysis with two main goals. First, we wanted to identify the prevalence of the delay of empiric antifungal treatment for patients with a *Candida* bloodstream infection until after the results of blood cultures were known. Our second goal was to determine whether the delay of the administration of antifungal treatment until the results of blood cultures were known influenced the clinical outcomes in patients with *Candida* bloodstream infections.

MATERIALS AND METHODS

Study location and patients. This study was conducted at a university-affiliated, urban teaching hospital: Barnes-Jewish Hospital (1,200 beds). During a 4-year period (January 2001 to December 2004), all hospitalized patients with a positive blood culture for *Candida* were eligible for this investigation. This study

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was approved by the Washington University School of Medicine Human Studies Committee.

Study design and data collection. A retrospective cohort study design was employed, with the main outcome measure being hospital mortality. We also assessed secondary outcomes, including microbiologic clearance of the infection, the duration of hospitalization, and the length of stay in the intensive care unit.

For all study patients, the following characteristics were recorded by one of the investigators (M.M.): age, gender, the presence of underlying malignancy, neutropenia, seropositivity for the human immunodeficiency virus antibody, diabetes mellitus, bone marrow or solid-organ transplant, abdominal or cardiothoracic surgery, and hypotension. These characteristics were determined at the time that the initial blood sample that was obtained for culture and from which a fungal pathogen was isolated was drawn. The white blood cell count, body temperature, and serum creatinine level were also assessed at the time that the initial positive blood samples for culture were collected and 72 h later. The severity of illness, based on Acute Physiology and Chronic Health Evaluation (APACHE) II scores (15), was calculated on the basis of clinical data available from the first 24-h period following identification of a positive blood culture result. The specific processes of medical care examined during the patients' hospital stays included mechanical ventilation for respiratory failure, the administration of vasopressors for circulatory shock, the presence of a central venous catheter and its duration of use prior to having a positive blood culture, the administration of parenteral nutrition, prior antimicrobial administration, prior antifungal therapy, and the number of ventilator days and intensive care unit days before the positive blood sample for culture was drawn. Variables describing the fungal bloodstream infection and their treatment were also assessed. All patient-level data were recorded from automated patient medical records (EMTEK Health Care Systems Inc., Tempe, AZ, and Clinical Desktop, BJC Healthcare, St. Louis, MO) and the Barnes-Jewish Hospital Pharmacy automated database, all of which contain prospectively entered information.

A computerized list of patients with a positive *Candida* blood culture was generated by the Microbiology Laboratory at Barnes-Jewish Hospital, which allowed identification of potential study patients. Patients could be entered into the study only once.

Definitions. All definitions were selected prospectively as part of the original study design. The timing of administration of antifungal therapy was determined as the interval between the time when the first *Candida*-positive blood sample for culture was drawn and the time when antifungal treatment was first administered to the patient. We segregated these times as being less than 12 h, 12 to 24 h, 24 to 48 h, or greater than 48 h.

The antimicrobial guideline employed for the empiric treatment of suspected nosocomial bloodstream infections at Barnes-Jewish Hospital recommends initial treatment with a combination of an antistaphylococcal drug (vancomycin for methicillin-resistant staphylococci) and at least one antibiotic, usually a beta-lactam, with activity against gram-negative bacteria (24). For patients at increased risk for infection with antibiotic-resistant gram-negative bacteria (e.g., *Pseudomonas aeruginosa* and *Acinetobacter* species), two antibiotics directed against gram-negative bacteria are initially recommended (an antipseudomonal beta-lactam or a carbapenem in combination with an aminoglycoside or a fluoroquinolone). The addition of empiric antifungal therapy is left to the discretion of the treating physicians, but treatment is recommended for high-risk patients (e.g., patients with prolonged neutropenia, prior antimicrobial exposure, or bowel perforation or patients receiving parenteral nutrition). The antibiotic guideline also recommends modification of the initially prescribed empiric antimicrobial regimens based on the results of clinical cultures and the antimicrobial susceptibilities of the pathogens identified. Deescalation or narrowing of the initial empirically prescribed antimicrobial regimens was routinely monitored by hospital pharmacists and had to be approved by the patient's primary physician team (13, 24).

For the purposes of this investigation, inappropriate antimicrobial treatment of a fungal bloodstream infection was defined as the microbiologic documentation of infection (i.e., a positive fungal blood culture result) that was not being effectively treated at the time that the causative microorganism was identified (12, 17, 19). Inappropriate antimicrobial treatment could occur due to omission of antifungal treatment or administration of an antifungal drug to which the fungal isolate was likely to be resistant. The microbiology laboratory at Barnes-Jewish Hospital does not perform routine antimicrobial susceptibility testing of fungal isolates. The use of fluconazole was assumed to be inappropriate if it was prescribed for fungal bloodstream infections caused by *Candida krusei* (9, 27, 35).

Hypotension was defined as mean arterial pressures lower than 55 mm Hg for at least 1 h, despite adequate fluid replacement and treatment with more than 5 μg/kg of body weight of dopamine or current treatment with epinephrine or norepinephrine (26). Additionally, urinary output of less than 0.5 ml/kg of body weight for at least 1 h was required as a definition of circulatory shock. Respiratory failure was defined as the need for mechanical ventilation applied either by an endotracheal tube or by a mask. The number of central vein catheter days prior to fungal bloodstream infection included the time from when the catheter was first placed, even if this preceded the current hospitalization.

Blood culture technique. Blood samples for culture were obtained from two peripheral sites by nurses or hospital-trained phlebotomists. Before collection of the blood samples, the skin was disinfected with 70% isopropyl alcohol, followed by 2% iodine tincture. The antecubital fossae were the preferred sampling sites, and sterile needles and syringes were used. When only one peripheral site was available and the patient had a central vein catheter in place, the second blood culture sample was obtained from the central vein catheter. Injection of 5 ml or less of blood into a blood culture bottle was not permitted to avoid false-negative results (38). All blood samples were inoculated into aerobic media and processed by using the BACTEC blood culture system (Becton Dickinson, Sparks, MD). BACTEC fungal medium bottles were available but had to be specifically requested by the physician ordering the blood cultures.

Statistical analysis. All comparisons were unpaired, and all tests of significance were two tailed. Continuous variables were compared by the Student *t* test for normally distributed variables and the Mann-Whitney U test for nonnormally distributed variables. The chi-square or Fisher's exact test was used to compare categorical variables. The primary data analysis compared hospital nonsurvivors with survivors. Values are expressed as the means ± standard deviations (continuous variables) or as a percentage of the group from which they were derived (categorical variables). All *P* values were two tailed, and *P* values of 0.05 or less were considered to indicate statistical significance.

We performed multiple logistic regression analysis using SPSS, version 11.0 for Windows (SPSS, Inc., Chicago, IL). Multivariable analysis was performed by using models that were judged a priori to be clinically sound (5). This was prospectively determined to be necessary to avoid the production of spuriously significant results with multiple comparisons. All potential risk factors significant at the 0.2 level were entered into the model. A stepwise approach was used to enter new terms into the logistic regression model, where hospital mortality was the dependent outcome variable, and 0.05 was set as the limit for the acceptance or removal of new terms.

RESULTS

Patients. A total of 157 consecutive patients with *Candida* bloodstream infections were evaluated. No patient with a *Candida* bloodstream infection was excluded from evaluation during this study period. The mean age of the patients was 56.0 ± 16.7 years (range, 19 to 97 years), and the mean APACHE II score was 13.9 ± 5.7 (range, 3 to 29). There were 79 (50.3%) men and 78 (49.7%) women; 34 (21.7%) patients were neutropenic, 36 (22.9%) had undergone either abdominal or cardiothoracic surgery, 31 (19.7%) had received an organ transplant, and 83 (52.9%) had an underlying malignancy (Table 1).

Patient characteristics according to hospital mortality. Fifty (31.8%) patients died during hospitalization. The 30-day mortality rate for this cohort of hospitalized patients was also 31.8%. Hospital nonsurvivors were statistically more likely than hospital survivors to have neutropenia, hypotension, and lower body temperature at the time that the initial positive blood samples for cultures were drawn; greater APACHE II scores; and higher serum creatinine values when positive blood samples for culture were initially drawn and 72 h later (Table 1). Additionally, hospital nonsurvivors more often required vasopressors, had more days on mechanical ventilation, and longer intensive care unit lengths of stay prior to the identification of a positive *Candida* blood culture than survivors (Table 2).

Fungal isolates and antimicrobial treatment characteristics. *Candida albicans* was the most common fungal isolate recovered from the blood cultures (Table 3). Six (3.8%) patients had two fungal species isolated from their blood cultures. Hospital

TABLE 1. Characteristics of culture-positive patients

Characteristic	Hospital survivors (n = 107)	Hospital nonsurvivors (n = 50)	P value
Age (yr)	55.3 ± 17.7[a]	57.4 ± 14.5	0.468
Gender (no. [%])			
Male	52 (48.6)	27 (54.0)	0.528
Female	55 (51.4)	23 (46.0)	
Underlying malignancy (no. [%])	53 (49.5)	30 (60.0)	0.221
HIV[b] positive (no. [%])	3 (2.8)	1 (2.0)	>0.999
Diabetes mellitus (no. [%])	11 (10.3)	4 (8.0)	0.651
Neutropenia (no. [%])	18 (16.8)	16 (32.0)	0.031
Surgery (no. [%])	28 (26.2)	8 (16.0)	0.158
Organ transplant (no. [%])	17 (15.9)	14 (28.0)	0.076
Mean arterial pressure <55 mm Hg (no. [%])	21 (19.6)	19 (38.0)	0.014
APACHE II score	12.3 ± 5.5	17.3 ± 4.8	<0.001
White blood cell count (10^9/liter)	9.4 ± 6.8	7.5 ± 8.3	0.041
White blood cell count at 72 h (10^9/liter)	8.9 ± 6.1	7.8 ± 7.3	0.188
Body temp (°C)	37.9 ± 1.2	37.4 ± 1.1	0.014
Body temp (°C) at 72 h	37.0 ± 0.8	36.9 ± 0.9	0.597
Serum creatinine level (mg/dl)	1.4 ± 1.2	2.1 ± 1.5	0.002
Serum creatinine level (mg/dl) at 72 h	1.5 ± 1.4	2.1 ± 1.2	0.001

[a] Values are presented as means ± standard deviations.
[b] HIV, human immunodeficiency virus.

TABLE 3. Fungal isolates from blood cultures

Fungal isolate	No. (%) of patients		
	Total	Hospital mortality	Inappropriate initial treatment[a]
Candida albicans	84 (53.5)	24 (28.6)	81 (96.4)
Candida parapsilosis	25 (15.9)	6 (24.0)	25 (100.0)
Candida glabrata	20 (12.7)	8 (40.0)	19 (95.0)
Candida tropicalis	20 (12.7)	10 (50.0)	19 (95.0)
Candida krusei	2 (1.3)	1 (50.0)	2 (100.0)
Candida albicans and *Candida glabrata*	3 (1.9)	0 (0.0)	3 (100.0)
Candida albicans and *Candida krusei*	2 (1.3)	1 (50.0)	2 (100.0)
Candida albicans and *Candida tropicalis*	1 (0.6)	0 (0.0)	1 (100.0)

[a] Inappropriate treatment was defined as the absence of antifungal agents at the time that fungus-positive blood samples for culture were drawn or fluconazole treatment with the subsequent isolation of either *Candida krusei* or *Candida glabrata*.

mortality was similar for patients with *Candida albicans* isolated from a blood culture and patients with non-*Candida albicans* species isolated from a blood culture (28.6% versus 35.6%; $P = 0.345$). Only five patients were treated with appropriate antifungal therapy at the time that the blood samples for culture were collected. One hundred thirty-four patients had empiric antifungal treatment started after the results of the fungal cultures were known. Among these 134 patients, 4 received empiric treatment with an agent to which the fungal isolate was presumed to be resistant.

From the time that a positive blood sample for culture was drawn, 9 (5.7%) patients received antifungal treatment within 12 h, 10 (6.4%) patients received antifungal treatment between 12 and 24 h, 86 (54.8%) patients received antifungal treatment between 24 and 48 h, and 52 (33.1%) patients received antifungal treatment after 48 h. The relationship between hospital mortality and the timing of the administration of antifungal treatment is shown in Fig. 1. Patients receiving antifungal treatment within 12 h of having a positive blood sample for culture drawn had a lower, but not statistically significantly different, risk of hospital mortality than patients begun on antifungal treatment after 12 h (11.1% versus 33.1%; $P = 0.169$). When the patients were stratified by severity of illness, patients receiving antifungal treatment within 12 h of having a positive blood sample for culture drawn also had a lower risk

TABLE 2. Processes of medical care for culture-positive patients

Process	Hospital survivor (n = 107)	Hospital nonsurvivors (n = 50)	P value
Corticosteroid treatment (no. [%])	26 (24.3)	19 (38.0)	0.077
Vasopressors (no. [%])	9 (8.4)	11 (22.0)	0.017
Central vein catheter (no. [%])	95 (88.8)	44 (88.0)	0.886
Central vein catheter days[a]	32.6 ± 46.5[b]	33.3 ± 54.2	0.928
Mechanical ventilator (no. [%])	21 (19.6)	14 (28.0)	0.240
Mechanical ventilator days[a]	1.7 ± 5.7	4.8 ± 12.0	0.033
Parenteral nutrition (no. [%])	31 (29.0)	9 (18.0)	0.142
ICU[c] days (no. [%])[a]	3.6 ± 9.4	6.6 ± 12.9	0.011
Hospital days (no. [%])[a]	12.2 ± 14.9	14.9 ± 13.2	0.109
Prior antimicrobial therapy (no. [%])	83 (77.6)	45 (90.0)	0.062
Prior antifungal therapy (no. [%])	10 (9.3)	2 (4.0)	0.341

[a] Assessed as days of exposure prior to having the first positive blood sample for culture drawn.
[b] Values are presented as means ± standard deviations.
[c] ICU, intensive care unit.

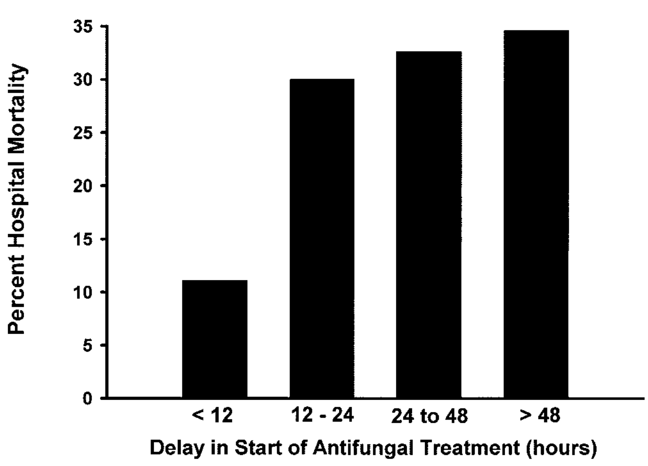

FIG. 1. Relationship between hospital mortality and the timing of antifungal treatment. The timing of antifungal therapy was determined to be from the time when the first blood sample for culture positive for fungi was drawn to the time when antifungal treatment was first administered to the patient.

TABLE 4. Multivariate analysis of independent risk factors for hospital mortality[a]

Variable	Adjusted odds ratio	95% Confidence interval	P value
APACHE II score (one-point increments)	1.24	1.18–1.31	<0.001
Prior antibiotic treatment	4.05	2.14–7.65	0.028
Delay in antifungal treatment	2.09	1.53–2.84	0.018

[a] Other covariates not present in the table had a P value greater than 0.05, including corticosteroid or vasopressor administration, neutropenia, organ transplant, serum creatinine level, and white blood cell count at the time of positive culture; surgery; parenteral nutrition; and the number of intensive care unit days before a fungus-positive blood sample for culture was drawn.

of mortality than patients begun on antifungal treatment after 12 h for patients with APACHE II scores less than or equal to 15 (n = 90) (0.0% versus 23.5%; P = 0.583) and for patients with APACHE II scores greater than 15 (n = 67) (25.0% versus 46.0%; P = 0.622).

Twenty-three (14.6%) patients received at least one dose of empiric appropriate antifungal treatment prior to notification of a positive *Candida* blood culture result. The hospital mortality rate for these patients was lower, but not statistically significantly different, than those for patients receiving appropriate antifungal treatment after notification of a positive blood culture result (21.7% versus 33.6%; P = 0.260). There was no statistical difference in APACHE II scores between patients receiving at least one dose of empiric appropriate antifungal treatment prior to notification of a positive *Candida* blood culture result and patients receiving appropriate antifungal treatment after notification of a positive blood culture result (14.9 ± 5.6 versus 13.8 ± 5.7; P = 0.375).

A similar analysis was conducted for the patients identified as having *Candida albicans*, *Candida parapsilosis*, or *Candida tropicalis* isolated from their blood cultures (n = 130). This was done, as these isolates are generally susceptible to fluconazole, eliminating the potential influence of fluconazole resistance in other strains of *Candida*. The hospital mortality was again found to be lower for patients receiving antifungal treatment within 12 h of having a positive blood sample for culture drawn (14.3% versus 31.7%; P = 0.437).

Multivariable analysis. Multiple logistic regression analysis identified increasing APACHE II scores (one-point increments), prior antibiotic treatment, and administration of antifungal treatment after 12 h of having the first positive blood sample for culture drawn as independent determinants of hospital mortality (Table 4). All other combinations of variables entered into the logistic regression analysis yielded a final model with administration of antifungal treatment after 12 h of having the first positive blood sample for culture drawn as an independent determinant of hospital mortality.

Secondary outcomes. Among the hospital nonsurvivors, the causes of death included sepsis and multiorgan failure not directly attributed to *Candida* infection (n = 31), sepsis and multiorgan failure directly attributed to *Candida* infection (n = 11), cardiac arrest (n = 6), and pulmonary embolism (n = 2). Patients receiving empiric antifungal treatment within 12 h of having blood samples for culture drawn had statistically shorter durations of mechanical ventilation and intensive care than patients receiving empiric antifungal treatment after 12 h of having blood samples for culture drawn. Hospital nonsurvivors had statistically longer durations of mechanical ventilation and intensive care unit lengths of stay (Table 5). Microbiologic clearance of the fungal pathogens and the overall duration of hospitalization did not differ between the survivors and the nonsurvivors. There were no statistically significant differences in any of the secondary outcome variables between patients infected with *Candida albicans* and patients infected with non-*C. albicans Candida* species. Among the 139 patients with a central vein catheter in place at the time that a positive blood sample for culture for *Candida* was drawn, the catheters were removed from 106 (76.3%) patients within 48 h of reporting of the positive blood culture result.

DISCUSSION

Our study demonstrated that initial empiric treatment of fungal bloodstream infection after 12 h of having the first positive blood sample for culture drawn is common and is associated with a greater risk of hospital mortality than treatment with appropriate antifungal agents within 12 h of having a positive blood sample for culture drawn. Multiple logistic regression analysis identified administration of antifungal therapy after 12 h of having the first positive blood sample for culture drawn as an independent predictor of hospital mortality. Additionally, our analysis showed that prior antimicrobial exposure and greater APACHE II scores were independently associated with hospital mortality.

Previous investigations have demonstrated that antimicrobial regimens lacking activity against the microorganisms that have been identified and that are causing serious infections (e.g., hospital-acquired pneumonia and bloodstream infections) are associated with greater rates of hospital mortality (11, 12, 17). More recently, the same finding has been demonstrated for patients with severe sepsis (8, 10). Inappropriate

TABLE 5. Secondary outcomes

Outcome	Antifungal treatment within 12 h (n = 9)	Antifungal treatment after 12 h (n = 148)	P value for time of antifungal treatment	Hospital survivors (n = 107)	Hospital nonsurvivors (n = 50)	P value for survival
Microbiologic clearance (no. [%])	9 (100.0)	145 (98.0)	0.550	106 (99.1)	48 (96.0)	0.238
Duration of mechanical ventilation (days)	0.0 ± 0.0[a]	7.0 ± 15.6	0.016	5.3 ± 15.8	9.4 ± 13.8	<0.001
Duration of intensive care (days)	0.4 ± 1.3	9.4 ± 19.4	0.019	7.4 ± 20.4	12.0 ± 15.2	<0.001
Hospital length of stay (days)	40.2 ± 18.1	31.4 ± 29.7	0.056	32.0 ± 32.8	31.8 ± 19.7	0.241

[a] Values are presented as means ± standard deviations.

antimicrobial treatment has been shown to be an important independent risk factor for mortality among hospitalized patients with serious infections, including bloodstream infections (12, 19). Unfortunately, changing of the antimicrobial therapy to an appropriate regimen after identification of a microorganism and its antimicrobial susceptibility has not been demonstrated to improve clinical outcomes (20, 32). These studies suggest that clinicians should strive to administer appropriate initial antimicrobial treatment to patients with serious infections, including fungal bloodstream infections, at the earliest time possible after suspecting the presence of infection. In addition to selecting an appropriate initial antimicrobial regimen, optimal dosing, an optimal interval of drug administration, and an optimal duration of treatment are required for antimicrobial efficacy, limiting toxicity, and prevention of the emergence of bacterial resistance (18).

Harbarth et al. examined 224 episodes of bloodstream infection among patients admitted to a surgical intensive care unit (11). They found that appropriate antimicrobial therapy was an independent determinant of survival and that mortality rates were highest for patients infected with pathogens causing infections most likely to be treated with inappropriate initial antimicrobial regimens (*Candida* species, *Enterobacter* species, and *Pseudomonas aeruginosa*). Similarly, we previously showed for individual microorganisms that there is a statistically significant correlation between the rates of inappropriate antimicrobial treatment for bloodstream infections and the associated hospital mortality rates (12). Fungal bloodstream infections had among the highest rates of inappropriate initial treatment and hospital mortality for all etiologic agents of bloodstream infections examined (12). Three recent studies of patients with severe sepsis, many of whom had bloodstream infections, including fungal bloodstream infections, also demonstrated that inappropriate initial antimicrobial therapy was associated with greater hospital mortality (6, 8, 10). These investigations support the importance of avoiding delays in the administration of appropriate antibiotics to patients with serious infections, including *Candida* bloodstream infections.

The studies that have evaluated inappropriate initial treatment for bloodstream infections suggest that the most common cause of inappropriate treatment for fungal bloodstream infections is the omission of initial empiric treatment (11, 12). An important problem preventing the earlier recognition and treatment of fungal bloodstream infections is the lack of specific clinical findings suggesting this diagnosis. Most authors recommend the use of clinical risk factors to identify patients at higher risk for fungal bloodstream infection (21, 30, 42). These risk factors can be used to identify patients who may benefit from empiric treatment for fungal bloodstream infection in the appropriate clinical setting. Additionally, the presence of prior antifungal treatment, especially with fluconazole, may identify patients who would potentially benefit from empiric treatment with alternative antifungal agents until the blood culture results become available (9, 35). Another approach is to consider the use of prophylactic antifungal treatment in high-risk patients in order to reduce the occurrence of fungal bloodstream infections (7, 22). Unfortunately, this approach still does not directly address the problem of treatment delays when fungal bloodstream infections eventually occur.

The more rapid diagnosis of *Candida* bloodstream infection may be the optimal method for avoiding delays in the treatment of this important infection. PCR is a method that has been evaluated to more rapidly identify the presence of *Candida* species, as well as other microorganisms, from clinical specimens, including blood, spinal fluid, and tissue biopsy specimens (23). Proteomics-based identification of novel *Candida* antigens for the diagnosis of systemic candidiasis offers an alternative potential approach to the more rapid diagnosis of this infection (31). Future clinical studies are needed to determine the overall operating characteristics of these diagnostic techniques and whether molecular diagnostics can be developed to be used cost-effectively in the clinical laboratory setting.

Our study has several important limitations. First, we did not identify risk factors for the development of fungal bloodstream infection. Earlier reports have demonstrated that prolonged hospitalization, prior treatment with antibiotics (particularly broad-spectrum antibiotics), and colonization with *Candida* species increase the likelihood of infection with this pathogen (4, 33, 40). The presence of such risk factors has been advocated as a trigger for the empiric treatment of potentially antibiotic-resistant bacteria and, when appropriate, fungal pathogens (18). Second, our study was performed at a single site, and the results may not be applicable to other settings. However, the consistent relationship between inappropriate treatment of serious infections and outcome that has been demonstrated suggests that this is a more universal finding, with applicability to patients with fungal bloodstream infections (11, 12). Third, we did not routinely perform susceptibility testing with the clinical isolates identified. Therefore, we could not determine the overall occurrence of inappropriate antifungal treatment when it was prescribed. Nevertheless, the main goal of our study was to evaluate the influence of temporal delays in the administration of antifungal treatment on patient outcomes. Fourth, we had only nine patients receiving appropriate antifungal treatment within 12 h of having a positive blood sample for culture drawn, which limits the generalization of our results. Finally, we were able to demonstrate by multivariable analysis a statistically significant relationship only between the administration of empiric antifungal treatment after 12 h from having a positive blood sample for culture drawn and hospital mortality. This underscores the complex nature of variables potentially influencing patient outcomes in the presence of serious infections.

In summary, we demonstrated that the administration of appropriate antimicrobial treatment more than 12 h after the first positive blood sample for culture is drawn is associated, at least by multivariable analysis, with hospital mortality. This underscores the clinical importance of providing early appropriate treatment to patients with fungal bloodstream infections. Future studies are needed to define the optimal strategy for the empiric treatment of fungal bloodstream infections. Until such data become available, clinicians may consider the use of empiric antifungal therapy in patients at high risk for this infection to avoid delays in treatment.

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